

IN THE SPECIFICATION

Amend the specification as follows.

Page 1, line 2, line 2, after the title, insert the following new paragraph:

The present application is a continuation of PCT Application No. PCT/EP99/05806, filed August 10, 1999, which designated the U.S., the entire contents of which is hereby incorporated by reference in this application.

Page 2, delete the paragraph spanning lines 10-23, and insert the following therefor:

Apart from exerting a plethora of effects mediated by the activation of its two types of receptors (TNF receptor 1, 55kD, and TNF receptor 2, 75 kD), TNF can also mediate receptor-independent activities. The tip domain of TNF is located on the top of its bell-shaped structure and is spatially distinct from its receptor binding sites, that are localized at the base of the trimeric molecule (Lucas *et al.*, 1994). This domain has lectin-like affinity for specific oligosaccharides, such as trimannose and diacetylchitobiose. Both TNF and the tip peptide of TNF are capable of mediating a trypanolytic activity by interfering with the lysosomal integrity of the trypanosome, a pH-dependent effect probably involving the insertion of TNF into the lysosomal membrane (Magez *et al.*, 1997). Moreover, mutants of the tip peptide in which three critical amino acids (T(105); E(107); E(110)) were replaced by A, were completely unable to mediate this activity (Lucas *et al.*, 1994). A mouse TNF (mTNF) triple mutant, ~~T105A-E107A-E110A~~ T104A-E106A-E109A (referred to hereafter as triple mTNF), lacks the

trypanolytic and lectin-like affinity to oligosaccharides as compared to wild type TNF.

The triple mTNF has significantly reduced systemic toxicity as compared to wild-type mTNF *in vivo*, but retains its peritonitis-protective effect in a murine model (Lucas *et al.*, 1997).

Delete the paragraphs spanning page 4, line 17 through page 5, line 21, and insert the following therefor:

The present invention relates to the use of a peptide comprising a chain of 7 to 17, preferably a chain of 11 to 16, more preferably a chain of 13 to 15 and most preferably a chain of 14 contiguous amino acids derived from the region of human TNF- α from Ser¹⁰⁰ to Glu¹¹⁶ or from the region of mouse TNF- α from Ser⁹⁹ to Glu¹¹⁵ for the manufacture of a medicament for treating oedema. More specifically the present invention relates to the use of a peptide as described above wherein said chain of 14 contiguous amino acids are chosen from the group consisting of the contiguous amino acid sequences QRETPEGAEAKPWY (SEQ ID NO:1) and PKDTPEGAEELKPWY (SEQ ID NO:2) as described by Lucas *et al.* (1994). The latter sequences are given in the well-known one-letter code for amino acids (the three-letter code is sometimes used further).

The term "peptide" refers to a polymer of amino acids (aa) derived from the trypanolytic TNF domain having lectin-like affinity as described by Lucas *et al.* (1994). Moreover, the latter term relates to a polymer of 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 or 17 contiguous amino acids derived from the region of human TNF- α from Ser¹⁰⁰ to Glu¹¹⁶ or from the region of mouse TNF- α from Ser⁹⁹ to Glu¹¹⁵. The latter TNF regions also refer to the regions shown in Fig. 5, p. 172 of Pennica and Goeddel in Webb and

Goeddel, eds. (1987). However, it should be clear that the region of human TNF- α from Ser¹⁰⁰ to Glu¹¹⁶ is identical to human TNF- α from Ser⁹⁹ to Glu¹¹⁶ in Fig. 5, p. 172 of Pennica and Goeddel in Webb and Goeddel, eds. (1987) and that the region of mouse TNF- α from Ser⁹⁹ to Glu¹¹⁵ is identical to mouse TNF- α from Ser⁹⁸ to Glu¹¹⁵ in Fig. 5, p. 172 of Pennica and Goeddel in Webb and Goeddel, eds. (1987). The term "peptide" more specifically relates to a peptide comprising the hexamer TPEGAE (SEQ ID NO:3) of the latter TNF regions or any peptide comprising the corresponding amino acids T, E and E of the latter hexamer which were shown to be three critical amino acids by Lucas *et al.* (1994). It should be clear that the present invention relates to any peptide derived from the latter TNF regions and does not exclude post-translational modifications of the peptides such as glycosylation, acetylation, phosphorylation, modifications with fatty acids and the like. Included within the present invention are, for example, peptides containing one or more analogues of an aa (including unnatural aa's), peptides with substituted linkages, mutated versions or natural sequence variations of the peptides, peptides containing disulfide bounds between cysteine residues, as well as other modifications known in the art. The peptides of the present invention are also defined functionally, that is, the present invention relates to any peptide which can be used to treat oedema or which can be used for the manufacture of a medicament for treating oedema. In essence, the present invention relates to any molecule, obtained by any method known in the art, with the same or very similar characteristics as the trypanolytic peptides defined by Lucas *et al.* (1994).

Delete the paragraph spanning page 5, line 29 through page 6, line 3, and insert the following therefor:

Furthermore, the present invention concerns the use of a peptide as described above wherein said peptide is circularized. More specifically, the present invention relates to the use of a peptide as described above, wherein said peptide is circularized by replacing the NH₂- and COOH-terminal amino acids by cysteine so that a disulfide bridge is formed between the latter cysteines. In this regard, the present invention concerns the use of a peptide as described above wherein said circularized peptides are chosen from the group consisting of the circularized peptides CGQRETPEGAEAKPWYC (SEQ ID NO:4) and CGPKDTPEGAELKPWYC (SEQ ID NO:5) as described by Lucas *et al.* (1994).

Delete the paragraphs spanning page 7, last line through page 8, line 3, and insert the following therefor:

Long tip peptide 99-115 (LTip)	GG-CGPKDTPEGAELKPWYC (<u>SEQ ID NO:6</u>)
Mutated tip peptide 99-115 (mutTip)	GG-CGPKD <u>A</u> P <u>A</u> G <u>A</u> ALKPWYC (<u>SEQ ID NO:7</u>)
Scrambled tip peptide (scambITip)	GG-CGTKPWELGPDEKPAYC(<u>SEQ ID NO:8</u>)
Short tip peptide (STip)	CTPEGAEC (<u>SEQ ID NO:9</u>)

Delete the paragraph spanning lines 19-31 of page 10 and insert the following therefor:

Since the lectin-like domain of TNF is spatially and functionally distinct from its receptor binding sites, we next investigated whether it was implicated in the observed

ion channel activating effect of TNF in mammalian cells. Therefore, the effect of a TNF mutant (mutTNF), in which the three critical residues for the lectin-like activity of TNF were replaced by an alanine ~~alanin~~, was compared with TNF in endothelial cells. As shown in Fig. 3, mutTNF completely lacked the conductance activating effect of TNF, even at a 100-fold higher dose (1 µg/ml mutTNF *versus* 10 ng/ml of TNF, data not shown). In contrast, the native and the mutated TNF molecules showed similar potencies in the induction of ICAM-1 in A549 epithelial cells (Fig. 4). This indicated that despite a conserved TNF receptor-mediated activity, mutTNF was unable to increase ion permeability. In order to test the hypothesis that TNF gated a sodium channel, we performed additional experiments in the presence of amiloride, an epithelial sodium channel blocker. One hundred µM amiloride added during the pretreatment at pH 6.0 abrogated the TNF-induced increase in conductance (Fig. 3).